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Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19 (Protocol)

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[Intervention Protocol]

Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects of chloroquine (CQ) and hydroxychloroquine (HCQ) as:

1. an antiviral treatment on death and time to clearance of the virus from clinical samples and recovery in people with COVID-19;
2. a prophylactic treatment on prevention of COVID-19 in people at risk of SARS-CoV-2 exposure;
3. a prophylactic treatment on prevention of COVID-19 in people who have been exposed to SARS-CoV-2.

BACKGROUND

Description of the condition

Coronavirus disease 2019 (COVID-19) is a viral infection transmitted by respiratory droplet spread and caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 commonly presents as a mild respiratory tract illness, with fever and cough the most commonly reported symptoms; however, in some people, this progresses to cause a life-threatening respiratory syndrome (Guan 2020).

SARS-CoV-2 is a novel coronavirus that has undergone widespread transmission since December 2019. Close to 2.5 million people have been diagnosed with COVID-19, and over 170,000 people have died as of 21 April 2020 (JHU 2020). The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020 (WHO 2020a).

National data from China and Italy describe severe disease in 14% to 20% of people with COVID-19, and a further 2% to 5% are reported to have critical illness (ISS 2020; Wu 2020). Mortality estimates range from around 2% to 12% (ISS 2020; Wu 2020). Severe disease is characterized by hypoxia and progressive acute respiratory distress syndrome appears to be the driver for mortality, although patients can experience a syndrome with clinical and laboratory features of severe systemic inflammation, termed a "cytokine storm" (Guan 2020; Mehta 2020).

At the other end of the spectrum, asymptomatic infection is not uncommon; national Italian data describes this in approximately 10% of all people with a confirmed COVID-19 diagnosis (ISS 2020).

Transmission is by direct contact with people with the infection, indirectly via contact with respiratory secretions on objects and surfaces, or from droplets generated by sneezing and coughing (WHO 2020b). Concerns have been raised about airborne transmission: viability of SARS-CoV-2 has been demonstrated for at least 3 hours when suspended in an aerosol (van Doremalen 2020). The amount of virus found in the respiratory tract appears to be higher in people with severe versus those with mild disease, with shedding of virus in the nasopharynx occurring for up to 25 days in people with severe disease (Liu 2020a). The virus has also been found in stools, with one study reporting live virus in non-diarrhoeal stool thus raising concerns about faecal-oral transmission (Wang 2020a).

Multiple episodes of transmission by pre-symptomatic or asymptomatic people have been described (Bai 2020; Rothe 2020).

The main method for diagnosis of COVID-19 is by polymerase chain reaction (PCR) of respiratory tract samples, mostly from the nasopharynx or oropharynx. However, some guidelines advise nasal swabs (CDC 2020), and some evidence suggests lower respiratory samples, such as sputum, may have higher sensitivity (Wang 2020a). While viraemia is rare, serological tests are being developed, using either antibody or antigen detection; it is hoped that a positive antibody test will confirm that someone has been previously infected with SARS-CoV-2 and is now immune (Amanat 2020).

Transmission is common in, though not limited to, households (Pung 2020). Self-isolation, quarantine, and travel restrictions can limit community transmission (Kraemer 2020), but prevention measures within households can be more challenging. Healthcare workers are at high risk of being infected. Data from Italy show that 20% of frontline healthcare workers responding to the pandemic have developed COVID-19 (Lancet 2020). There is widespread shortage of personal protective equipment, and there are concerns about airborne transmission (Lewis 2020). With established community transmission in many countries, healthcare workers are also at risk outside of health facilities. With vaccines entering trial stage but unlikely to report clinical data within a few months, there is great interest in chemoprophylaxis for prevention of COVID-19.

Several potential antivirals have been suggested for treating people with COVID-19, with studies attempting to demonstrate effectiveness of the influenza treatments arbidol (Deng 2020) and favipiravir (Cai 2020); and the antiretroviral protease inhibitor combination lopinavir/ritonavir (Cao 2020). Remdesivir, a drug trialled for Ebola virus disease and Middle East respiratory syndrome (MERS), has shown promising results in vitro (Wang 2020b). Multiple trials have been set up to establish evidence for effectiveness of these in patients with COVID-19. Many other options are being investigated, including corticosteroids (EudraCT 2020-001113-21), tocilizumab (Xu 2020), convalescent plasma (Shen 2020), and camostat mesylate (Hoffman 2020). Research groups have been using novel methods to assess whether existing drugs can be repurposed for COVID-19 treatment (Chandel 2020; Zhou 2020).

Description of the intervention

Chloroquine (CQ) and hydroxychloroquine (HCQ) are 4-aminoquinoline compounds, derivatives of quinine, and have been used as antimalarial drugs since the 1940s (Ben-Zvi 2012). HCQ is an analogue of CQ in which one of the N-ethyl substituents of CQ is β-hydroxylated. HCQ and CQ have similar pharmacokinetic properties, with high oral bioavailability and tissue penetrance, partial hepatic metabolism, and high volumes of distribution as they diffuse into adipose tissue (Ben-Zvi 2012).

Both drugs have been used widely and for many years for treatment and prophylaxis of malaria and treatment of rheumatological conditions, such as systemic lupus erythematosus and rheumatoid arthritis (Steinhardt 2011; Fiehn 2020).

The mechanism of action in the treatment and prevention of malaria is thought to result from inhibition of the biocrystallization of hemozoin, causing cytotoxic accumulation of heme (Schrezenmeier 2020). For rheumatological conditions, the mechanism of action is not fully delineated, but appears to arise from multiple effects. As weak bases, both CQ and HCQ accumulate in the acidic environment within lysosomes, and thus interfere with lysosomal activity and autophagy, which in turn may inhibit major histocompatibility complex (MHC) class II expression and antigen presentation, inhibiting immune activation (Schrezenmeier 2020). CQ and HCQ also interfere with Toll-like receptor (TLR) signalling, again via changes to local pH but also through direct binding to nucleic acids. TLR signal pathways stimulate cytokine production, and CQ and HCQ have been demonstrated to inhibit production of various cytokines including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF), and interferon gamma (IFNγ) by mononuclear cells (van den Borne 1997).

CQ and HCQ have well-described adverse effect profiles. Common adverse effects include gastrointestinal upset and headache (Ben-

Zvi 2012). Several adverse effects are associated with chronic therapy, such as QT interval prolongation on electrocardiogram, other cardiac arrhythmia, and retinopathy (Fiehn 2020). CQ is generally less tolerable than HCQ, and can cause acute poisoning at a lower dose, as has been seen in reports from the USA and Nigeria of members of the public taking CQ without a prescription (CNN 2020; Owens 2020).

There are two types of CQ salts: CQ phosphate and CQ sulphate. Most dosing recommendations for CQ refer to the salt rather than the base compound. Usual doses for CQ are 250 mg to 500 mg CQ phosphate (155 mg to 310 mg CQ base) per dose, or CQ sulphate 200 mg (150 mg CQ base), with weekly dosing for malaria prophylaxis, and daily dosing for treatment of malaria and rheumatological conditions. HCQ is given at a dose of 400 mg weekly for malaria prophylaxis, and 200 mg to 400mg daily for rheumatological disease (Ben-Zvi 2012).

How the intervention might work

Both CQ and HCQ have been suggested as agents for treatment and prevention of COVID-19. Studies have reported in vitro activity against SARS-CoV-2 (Liu 2020b; Wang 2020b; Yao 2020), and pharmacokinetic modelling suggests efficacy of a few postulated dosing regimens for treatment (Yao 2020).

Liu 2020b reported that CQ and HCQ appear to inhibit transport of SARS-CoV-2 virions from early endosomes to endolysosomes in Vero E6 cells, which may be a requirement for release of the viral genome and subsequent viral replication. Wang 2020b performed a "time-to-addition" assay using Vero E6 cells, and found that CQ appeared to both inhibit entry of SARS-CoV-2 into cells, and inhibit viral replication after cell entry. The authors of both studies also speculate that CQ and HCQ could impact on disease severity in CoVID-19 through modulating the excess cytokine release that appears to contribute to life-threatening forms of the disease (Liu 2020b; Wang 2020b).

Why it is important to do this review

Given the pace of the pandemic, and the extraordinary impact on public health and society in many countries, there is high demand for effective prevention and treatment for COVID-19. CQ and HCQ are cheap drugs that are registered in most countries, and are included on the WHO essential medicines list (WHO 2019). They can be delivered orally, and both drugs have well-described safety profiles in adults and children. Given the lack of effective antiviral drugs that can treat COVID-19, or an effective vaccine, identifying existing medicines that may be of benefit is of high importance. Despite the small number of published studies, some governments have already recommended using HCQ as prophylaxis for healthcare workers, and some prominent political figures have asserted that CQ or HCQ should be used as a first-line treatment for COVID-19. Sadly, there have already been instances of significant harm where individuals have misinterpreted news stories about the use of CQ, and suffered toxicity.

Several national guidelines are recommending CQ or HCQ for treatment of patients with COVID-19. Belgian guidelines recommend HCQ for severe disease, and advise to consider HCQ for mild-moderate disease (WIV-ISP 2020); Chinese guidelines advise consideration of CQ in all hospitalized patients, although later iterations have expressed caution regarding dosing and special patient groups (Wong 2020); Italian guidelines recommend early use of CQ or HCQ, or lopinavir/ritonavir (Brescia-COVID Group 2020). The WHO, the US Centers for Disease Control and Prevention (CDC), and Public Health England are yet to recommend CQ or HCQ for treatment.

Most guidelines cite interim results of two studies. A brief letter on 19 February 2020 reported that a news briefing on 17 February stated that "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course", but results are yet to be published as of 21 April 2020 (Gao 2020). A small non-randomized study of hospitalized patients in Marseille, France, reported that HCQ was associated with earlier negative nasopharyngeal PCR for SARS-CoV-2 among 20 patients given 200 mg three times per day for 10 days compared to patients not receiving HCQ (Gautret 2020a). Participants were included if they had a positive PCR test for SARS-CoV-2, were aged ≥12 years, had no allergy/contraindication to HCQ, and were not pregnant/breastfeeding. Of 42 initial participants, 36 were included in the final analysis: six (all in the HCQ arm) were removed due to loss to follow-up within three days of enrolment, including three who were transferred for intensive care and one who died. The 36 participants included eight participants with lower respiratory tract infection and six participants with asymptomatic disease; most (22/36) had upper respiratory tract symptoms (Gautret 2020a). The control group (16 participants) comprised those who had refused to take HCQ or had presented to other hospitals. Virological clearance (defined as negative PCR for SARS-CoV-2) at day 6 post-enrolment was 14/20 (70%) in the HCQ arm, and 2/16 (12.5%) in the group not receiving HCQ. Subgroup analyses appeared to show a statistically significant increase in virological clearance for six participants who had azithromycin in combination with HCQ (Gautret 2020a). The study authors did not present clinical efficacy or safety data, and no effect estimates nor confidence intervals (CIs) were reported. The study was also underpowered in terms of sample size.

The presentation of individual patient data in a supplementary table has allowed further analyses to be conducted (Gautret 2020a). One preprint publication reports re-analysis of the data using regression and survival models, showing wide CIs for effect size estimates (Lover 2020). The author recommends larger randomized trials, but interprets the survival model re-analysis results to show greater promise of the combination of HCQ plus azithromycin versus neither drug (Lover 2020). Another preprint applies Bayesian methods to the original data, showing a lack of robustness to assumptions about participants lost to follow-up and the four with unfavourable clinical outcomes in the HCQ group (Hulme 2020). The authors caution against concluding efficacy of HCQ or its combination with azithromycin (Hulme 2020).

Following results of the non-randomized study above, the same research group from France has published a preprint of an observational single-arm cohort of 80 patients given HCQ plus azithromycin (Gautret 2020b). They provide limited clinical outcome data: 65/80 patients showed clinical improvement (Gautret 2020b). A table in this preprint mentions blurred vision as an adverse event in one patient after five days of treatment, without further details; this is of concern, due to HCQ's association with retinopathy (Gautret 2020b).

Another research group from France advise caution in the use of this combination of HCQ and azithromycin in their journal preproof case series, and report much poorer clinical and virological outcomes in 11 hospitalized patients treated with both drugs (Molina 2020). Of their patients, 8/11 had co-morbidities and 10/11 were receiving oxygen therapy. Over five days, one patient died, two were transferred to the intensive care unit, and another patient had to discontinue therapy due to prolongation of QTc interval on electrocardiography. Of 10 patients alive at five days, eight had a positive PCR for SARS-CoV-2 RNA on nasopharyngeal swabs at 5 to 6 days after commencing treatment (Molina 2020).

Two small randomized trials of HCQ have reported recently from China, with mixed results (Chen 2020a; Chen 2020b). Of the trials underway, some are large multicentre multi-arm RCTs coordinated/funded by the WHO (ISRCTN83971151), UK National Institute of Health Research (EudraCT 2020-001113-21), and the US National Institutes of Health (NCT04280705).

There are currently no studies with human participants reporting use of CQ or HCQ for prophylaxis of COVID-19. Several trials exploring use of CQ or HCQ for prophylaxis of COVID-19 are underway (Cortegiani 2020; Mitjà 2020). Despite lack of data on prophylaxis, the Indian Council of Medical Research has already recommended HCQ as pre-exposure prophylaxis for frontline healthcare workers having “high-risk” contact with patients with suspected or confirmed COVID-19, and post-exposure prophylaxis for household and healthcare worker contacts of patients with confirmed COVID-19 (ICMR 2020). The background section of this recommendation states there is in vivo evidence for efficacy of HCQ for treatment of COVID-19, and prophylactic efficacy is inferred from therapeutic efficacy (ICMR 2020).

Systematic reviews of the evidence for CQ and HCQ in COVID-19 have been produced elsewhere. A systematic review of CQ for treatment of COVID-19, which searched PubMed and Embase up to 1 March 2020, identified no published studies other than the aforementioned letter (Gao 2020); though 23 clinical trials of CQ or HCQ were found on registries (Cortegiani 2020) Another systematic review of CQ and HCQ for treating COVID-19, published as a preprint on 30 March 2020, concluded: “There is theoretical, experimental, preclinical and clinical evidence of the effectiveness of chloroquine in patients affected with COVID-19” (Kapoor 2020). A further review included one non-randomized study and one randomized trial, and concluded "Without further evidence, HCQ is not appropriate for patients with COVID-19 in primary care" (McCormack 2020). A systematic review of antimalarials (CQ and HCQ) for treatment of COVID-19 was produced by the Epistemonikos Working Group. They synthesized results of two small randomized trials, finding low to very low certainty evidence regarding efficacy and harms (Epistemonikos 2020).

We propose that, in this context, a systematic review using standard Cochrane methods that provides summary estimates of effects for both treatment and prophylactic use of CQ and HCQ, with an appraisal of the certainty of the evidence using the GRADE approach, is important for the general public, clinicians, and policymakers. We plan to update this review in an expedited fashion as new data becomes available from the trials that are currently in progress.

OBJECTIVES

To evaluate the effects of chloroquine (CQ) and hydroxychloroquine (HCQ) as:

1. an antiviral treatment on death and time to clearance of the virus from clinical samples and recovery in people with COVID-19;
2. a prophylactic treatment on prevention of COVID-19 in people at risk of SARS-CoV-2 exposure;
3. a prophylactic treatment on prevention of COVID-19 in people who have been exposed to SARS-CoV-2.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Objective 1. People who have COVID-19, as defined by study authors.

Objective 2. People who are at risk of SARS-CoV-2 exposure, as defined by study authors.

Objective 3. People who have been exposed to SARS-CoV-2, as defined by study authors.

Types of interventions

Intervention

Chloroquine (CQ) or hydroxychloroquine (HCQ) given by any route of administration and dose used alone or in combination with other treatments.

Control

No treatment, supportive treatment, or other experimental antiviral treatment.

Types of outcome measures

The outcomes of interest are different for CQ/HCQ used to treat COVID-19 disease, and for CQ/HCQ used as pre- or post-exposure prophylaxis to prevent COVID-19 disease.

Objective 1. For treatment of COVID-19 disease

Primary outcomes

- Death
- Time to negative PCR for SARS-CoV-2 on respiratory samples

Secondary outcomes

- Number of participants admitted to hospital (if receiving ambulatory treatment)
- Number of participants requiring mechanical ventilation
- Length of hospital admission
- Time to clinical improvement, as defined by study authors
- Duration of mechanical ventilation post-enrolment in survivors of COVID-19

Objective 2. For prevention of COVID-19 disease in people at risk of exposure to SARS-CoV-2

Primary outcomes

- Development of confirmed COVID-19, as defined by study authors
- Production of antibodies to SARS-CoV-2

Secondary outcomes

- Development of COVID-19 in household contacts of the recipient of the prophylaxis
- Disease severity of participants who develop COVID-19, as defined by study authors

Objective 3. For prevention of COVID-19 disease in people who have been exposed to SARS-CoV-2

Primary outcomes

- Development of COVID-19confirmed COVID-19, as defined by study authors
- Production of antibodies to SARS-CoV-2

Secondary outcomes

- Development of COVID-19 in household contacts of the recipient of the prophylaxis
- Disease severity of participants who develop COVID-19, as defined by study authors

Adverse events (relating to objectives 1, 2, and 3)

- All adverse events
- All serious adverse events attributed to study drug (that is, serious adverse effects)
- QT-interval prolongation

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); and Embase (OVID). We will also search Current Controlled Trials (www.controlled-trials.com) using 'chloroquine', 'hydroxychloroquine', 'coronavirus', and 'COVID-19' as search terms; and we will search COVID-specific resources www.covid-nma.com and https://covid-19.cochrane.org/, which are updated daily with lists of ongoing and published trials.

Searching other resources

We will contact researchers in the field to identify unpublished or ongoing studies.

Data collection and analysis

For selection of studies and data extraction, two review authors (BS and HR) will independently conduct each step, and examine agreement between them. We will resolve any disagreements through discussion.

Selection of studies

Two review authors (BS and HR or MC) will independently screen the search results using Covidence (Covidence 2020), and will retrieve the full-text articles of all potentially relevant trials. We will examine each trial report to ensure that we include multiple publications from the same trial only once. We will contact trial authors for clarification if a trial's eligibility is unclear. We will resolve any disagreements through discussion, and will list the excluded studies and the reasons for their exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (BS and HR, MC, or TK) will use a pre-piloted data extraction form to extract data on participant characteristics, diagnostic criteria, disease severity, pre-morbid functional status and co-morbidity, CQ or HCQ dose and administration, other treatments given, and outcome measures. We will resolve disagreements through discussion, and will contact the corresponding trial author in the case of unclear or missing data.

For dichotomous outcomes, we will record the number of participants that experienced the event and the number of participants randomized to each treatment group, and will use them in the analysis. We will record the number of participants analysed in each treatment/prophylaxis arm, and use the discrepancy between the figures to calculate the number of participants lost to follow-up, which will allow us to perform sensitivity analyses to investigate the effect of missing data.

Assessment of risk of bias in included studies

Two review authors (BS and HR, MC, or TK) will assess methodological quality using the Cochrane 'Risk of bias' tool and report the results in a 'Risk of bias' table (Higgins 2011). We will classify each domain as either at high, low, or unclear risk of bias (Higgins 2011). We will assess the risk of bias associated with blinding separately for each outcome; for other domains we will assess the risk of bias for the trial as a whole. We will attempt to contact the trial authors if information is not specified or is unclear. We will resolve any disagreements by discussion between the review authors.

Measures of treatment effect

We will present dichotomous outcomes as risk ratios (RR) and 95% confidence intervals (CIs). We will report continuous outcomes as mean differences (MD) and 95% CIs if the outcomes have been measured in the same way across all included trials. In the case that included trials measured continuous outcomes in different ways, we will use the standardized mean difference (SMDs) and 95% CI as the effect measure. We will present time-to-event outcomes as hazard ratios and 95% CIs.

Unit of analysis issues

We do not anticipate that any cluster-randomized studies will meet the inclusion criteria of this review. If we identify cluster-randomized studies that meet the inclusion criteria, we will ensure appropriate analysis adjusting for the effect of cluster randomization is carried out before including effects estimates in a meta-analysis. If available, we will extract adjusted measures of

effect from the trial reports. If only unadjusted data are available, we will adjust this data ourselves using the intracluster correlation coefficient (ICC). If the ICC is not reported, we will contact the study authors to obtain this, or will borrow an ICC value from a similar study, or will estimate the ICC. If the ICC is estimated, we will perform sensitivity analyses to investigate the robustness of our analyses.

If we identify multi-arm trials, we will either select relevant arms for inclusion in our analyses, or if more than two arms are relevant to this review, we will either combine intervention arms so that there is one comparison, or split the control group between multiple comparisons so that participants are not double-counted in meta-analysis.

Dealing with missing data

The primary analysis for all outcomes will be an available case analysis where the denominator is the number of patients completing follow-up to the point of outcome assessment. We will carry out sensitivity analyses to explore the impact of missing data on the primary outcomes. For dichotomous outcomes, we will vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data we will also perform sensitivity analyses using methods described by Ebrahim 2013 and Ebrahim 2014.

Assessment of heterogeneity

We will assess heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of CIs. We used the Chi^2 test with a P value of 0.10 to indicate statistical significance, and the I^2 statistic to assess heterogeneity with a value of 50% taken to indicate statistical heterogeneity.

Assessment of reporting biases

We will construct a funnel plot to investigate any potential reporting bias if we have 10 or more studies included for an outcome.

Data synthesis

We will analyse the data using Review Manager 5 (RevMan 5) (Review Manager 2014). In the absence of substantial clinical or methodological heterogeneity we will perform a meta-analysis, using risk ratios (RR) with 95% CIs and a random-effects model. Where a meta-analysis is not appropriate, we will summarize data in tables.

Subgroup analysis and investigation of heterogeneity

We plan to investigate heterogeneity by performing the following subgroup analyses for people with COVID-19:

- Disease severity at presentation
- Time in the illness when treatment started (< 7 days, and ≥ 7 days after symptoms started)
- Co-morbidity, such as cardiovascular disease, diabetes, and immunosuppression
- Age
- Sex
- Admitted to hospital versus receiving ambulatory/outpatient treatment
- CQ or HCQ dosing regimen

We plan to investigate heterogeneity by performing the following subgroup analyses for people exposed to SARS-CoV-2 or at risk of exposure to SARS-CoV-2:

- Healthcare workers
- Household contacts
- Laboratory staff
- Age
- Co-morbidity, such as cardiovascular disease, diabetes, and immunosuppression

Sensitivity analysis

To explore the possible effect of losses to follow-up on the effect estimates for the primary outcomes, we will perform sensitivity analyses. For dichotomous outcomes, we will vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data we will perform sensitivity analyses using methods described by Ebrahim 2013 and Ebrahim 2014.

Summary of findings and assessment of the certainty of the evidence

We will summarize the results of the analysis in 'Summary of findings' tables for each of the two objectives, and will present the summary effects estimates for the primary outcomes with illustrative comparative risks. We will use the GRADE framework to evaluate the certainty of evidence for each outcome, as developed by the GRADE Working Group and described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

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REFERENCES

Additional references

Amanat 2020

Amanat F, Stadlbauer D, Strohmeier S, Nguyen T, Chromikova V, McMahon M, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. medRxiv pre-print: 16 April 2020. www.medrxiv.org/content/10.1101/2020.03.17.20037713v1 (accessed 20 April 2020). [DOI: 10.1101/2020.03.17.20037713]

Bai 2020

Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA* 2020;**323**(14):1406-7. [DOI: 10.1001/jama.2020.2565]

Ben-Zvi 2012

Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clinical Reviews in Allergy & Immunology* 2012;**42**(2):145-53. [DOI: 10.1007/s12016-010-8243-x]

Brescia-COVID Group 2020

Brescia-COVID Group. Brescia-COVID Respiratory Severity Scale Algorithm. Step-wise management approach to COVID-19 patients based on clinical severity as of March 27, 2020. www.mdcalc.com/brescia-covid-respiratory-severity-scale-bcrss-algorithm (accessed 6 April 2020).

Cai 2020

Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020 March 18 [Epub ahead of print] (accessed 21 April 2020). [DOI: 10.1016/j.eng.2020.03.007]

Cao 2020

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine 2020 March 18 [Epub ahead of print]. [DOI: 10.1056/NEJMoa2001282]

CDC 2020

Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for Coronavirus Disease 2019 (COVID-19). 14 April 2020. www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html (accessed 20 April 2020).

Chandel 2020

Chandel V, Raj S, Rathi B, Kumar D. In silico identification of potent COVID-19 main protease inhibitors from FDA approved antiviral compounds and active phytochemicals through molecular docking: a drug repurposing approach. www.preprints.org/manuscript/202003.0349/v1 2020 March 23 (accessed 6 April 2020). [DOI: 10.20944/preprints202003.0349.v1]

Chen 2020a

Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Journal of Zhejiang University 2020 March 3 [Epub ahead of print]. [DOI: 10.3785/j.issn.1008-9292.2020.03.03]

Chen 2020b

Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Posted April 10, 2020. www.medrxiv.org/content/10.1101/2020.03.22.20040758v2 (accessed 20 April 2020). [DOI: 10.1101/2020.03.22.20040758]

CNN 2020

Busari S, Adebayo B, CNN. Nigeria records chloroquine poisoning after Trump endorses it for coronavirus treatment. 23 March 2020. https://edition.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html (accessed 14 April 2020).

Cortegiani 2020

Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of Critical Care 2020 March 10 [Epub ahead of print]. [DOI: 10.1016/j.jcrc.2020.03.005]

Covidence 2020 [Computer program]

Veritas Health Innovation. Covidence. Version accessed 6 April 2020. Melbourne, Australia: Veritas Health Innovation.

Deng 2020

Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. Journal of Infection 2020 March 11 [Epub ahead of print]. [DOI: 10.1016/j.jinf.2020.03.002]

Ebrahim 2013

Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, et al. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. *Journal of Clinical Epidemiology* 2013;**66**(9):1014-21.e.1. [DOI: 10.1016/j.jclinepi.2013.03.014]

Ebrahim 2014

Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. *Journal of Clinical Epidemiology* 2014;**67**(5):560-70. [DOI: 10.1016/j.jclinepi.2013.11.014]

Epistemonikos 2020

Epistemonikos COVID-19 L.OVE Working Group. Antimalarials for the treatment of COVID-19: Systematic review - preliminary report. Last update: 31 March 2020. www.epistemonikos.cl/2020/03/27/systematic-review-preliminary-report-antimalarials-for-the-treatment-of-covid-19/ (accessed 7 April 2020).

EudraCT 2020-001113-21

EudraCT 2020-001113-21. Randomised Evaluation of COVID-19 Therapy (RECOVERY). www.clinicaltrialsregister.eu/ctr-search/

trial/2020-001113-21/GB (first entered 19 March 2020). [EudraCT 2020-001113-21]

Fiehn 2020

Fiehn C, Ness T, Weseloh C, Specker C, Hadjiski D, Detert J, et al. Safety management in treatment with antimalarials in rheumatology. Interdisciplinary recommendations on the basis of a systematic literature review. Zeitschrift fur Rheumatologie 2020 March 31 [Epub ahead of print]. [DOI: 10.1007/s00393-020-00785-4]

Gao 2020

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends* 2020;**14**(1):72-3. [DOI: 10.5582/bst.2020.01047]

Gautret 2020a

Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 2020 March 20 [Epub ahead of print]. [DOI: 10.1016/j.ijantimicag.2020.105949]

Gautret 2020b

Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf (accessed 6 April 2020).

Guan 2020

Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine 2020 Feb 28 [Epub ahead of print]. [DOI: 10.1056/NEJMoa2002032]

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hoffman 2020

Hoffman M, Kleine-Weber H, Schroeder S, Krüger N, Herrier T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020;**181**(2):271-80.e.8. [DOI: 10.1016/j.cell.2020.02.052]

Hulme 2020

Hulme OJ, Wagenmakers E-J, Damkier P, Madelung CF, Siebner HR, Helweg-Larsen J, et al. Reply to Gautret et al. 2020: A Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin on viral carriage in patients with COVID-19. www.medrxiv.org/content/10.1101/2020.03.31.20048777v1 3 April 2020 (accessed 6 April 2020). [DOI: 10.1101/2020.03.31.20048777]

ICMR 2020

Indian Council of Medical Research – National Taskforce for COVID-19. Recommendation on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. 22 March 2020. https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf (accessed 6 April 2020).

ISRCTN83971151

ISRCTN83971151. Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients. www.isrctn.com/ISRCTN83971151 (date applied 25 March 2020). [ISRCTN83971151]

ISS 2020

Istituto Superiore di Sanità. Sorveglianza integrata COVID-19 in Italia. 5 April 2020. www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati (accessed 6 April 2020).

JHU 2020

Dong E, Du H, Gardner L, on behalf of Johns Hopkins University Centre for Systems Science and Engineering. An interactive web-based dashboard to track COVID-19 in real time. Published online 19 February 2020. Lancet Infectious Diseases (accessed 21 April 2020). [DOI: 10.1016/S1473-3099(20)30120-1]

Kapoor 2020

Kapoor KM, Kapoor A. Role of chloroquine and hydroxychloroquine in the treatment of COVID-19 infection- a systematic literature review. www.medrxiv.org/content/10.1101/2020.03.24.20042366v1 30 March 2020 (accessed 6 April 2020). [DOI: 10.1101/2020.03.24.20042366]

Kraemer 2020

Kraemer MUG, Yang C-H, Gutierrez B, Wu C-H, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. Science 25 March 2020 (accessed 6 April 2020). [DOI: 10.1126/science.abb4218]

Lancet 2020

Lancet. COVID-19: protecting health-care workers. *Lancet* 2020;**395**(10228):922. [DOI: 10.1016/S0140-6736(20)30644-9]

Lewis 2020

Lewis D. Is the coronavirus airborne? Experts can't agree. www.nature.com/articles/d41586-020-00974-w (accessed 6 April 2020). [DOI: 10.1038/d41586-020-00974-w]

Liu 2020a

Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infectious Diseases 19 March 2020 (accessed 6 April 2020). [DOI: 10.1016/S1473-3099(20)30232-2]

Liu 2020b

Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery* 2020;**6**:16. [DOI: 10.1038/s41421-020-0156-0]

Lover 2020

Lover AA. Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al, 2020). Posted April 10, 2020. www.medrxiv.org/content/10.1101/2020.03.22.20040949v1 (accessed 20 April 2020). [DOI: 10.1101/2020.03.22.20040949]

McCormack 2020

McCormack J, Lindblad AJ. Hydroxychloroquine with or without azithromycin for COVID-19. Published 30 March 2020. gomainpro.ca/tools-for-practice/articles/details/?id=619&page-title=Hydroxychloroquine+with+or+without+azithromycin+for+COVID-19 (accessed 7 April 2020).

Mehta 2020

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**(10229):1033-4. [DOI: 10.1016/S0140-6736(20)30628-0]

Mitjà 2020

Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Global Health 2020 March 19 [Epub ahead of print]. [DOI: 10.1016/S2214-109X(20)30114-5]

Molina 2020

Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine et Maladies Infectieuses 2020 March 30 [Epub ahead of print]. [DOI: 10.1016/j.medmal.2020.03.006]

NCT04280705

NCT04280705. Adaptive COVID-19 Treatment Trial (ACTT). https://clinicaltrials.gov/ct2/show/NCT04280705 (first posted 21 February 2020). [NCT04280705]

Owens 2020

Owens B. Excitement around hydroxychloroquine for treating COVID-19 causes challenges for rheumatology. Lancet Rheumatology 2020 April 1 [Epub ahead of print]. [DOI: 10.1016/S2665-9913(20)30089-8]

Pung 2020

Pung R, Chiew CJ, Young BE, Chin S, Chen MI-C, Clapham HE, et al. Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures. *Lancet* 2020;**395**(10229):1039-46. [DOI: 10.1016/S0140-6736(20)30528-6]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rothe 2020

Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an asymptomatic contact in Germany. *New England Journal of Medicine* 2020;**382**:970-1. [DOI: 10.1056/NEJMc2001468]

Schrezenmeier 2020

Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nature Reviews. Rheumatology* 2020;**16**(3):155–66. [DOI: 10.1038/s41584-020-0372-x]

Shen 2020

Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 March 27 [Epub ahead of print]. [DOI: 10.1001/jama.2020.4783]

Steinhardt 2011

Steinhardt LC, Magill AJ, Arguin PM. Review: Malaria chemoprophylaxis for travelers to Latin America. *American Journal of Tropical Medicine and Hygiene* 2011;**85**(6):1015–24. [DOI: 10.4269/ajtmh.2011.11-0464]

van den Borne 1997

van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *Journal of Rheumatology* 1997;**24**(1):55-60. [PUBMED: 9002011]

van Doremalen 2020

van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *New England Journal of Medicine* 2020;**382**(16):1564-7. [DOI: 10.1056/NEJMc2004973]

Wang 2020a

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020 March 11 [Epub ahead of print]. [DOI: 10.1001/jama.2020.3786]

Wang 2020b

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 2020;**30**(3):269–71. [DOI: 10.1038/s41422-020-0282-0]

WHO 2019

World Health Organization. WHO Model List of Essential Medicines, 21st List. www.who.int/medicines/publications/essentialmedicines/en (accessed 21 April 2020).

WHO 2020a

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 76. www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed 6 April 2020).

WHO 2020b

World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Published 28 February 2020. www.who.int/publications-detail/report-

of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19) (accessed 6 April 2020).

WIV-ISP 2020

WIV-ISP (Scientific Institute of Public Health, Belgium). Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium. https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf 31 March 2020 (accessed 6 April 2020).

Wong 2020

Wong YK, Yang J, He K. Caution and clarity required in the use of chloroquine for COVID-19. Lancet Rheumatology 2020 April 2 [Epub ahead of print]. [DOI: 10.1016/S2665-9913(20)30093-X]

Wu 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42. [DOI: 10.1001/jama.2020.2648]

Xu 2020

Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv:202003.00026 (pre-print) 5 March 2020 (accessed 6 April 2020).

Yao 2020

Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases 2020 March 9 [Epub ahead of print]. [DOI: 10.1093/cid/ciaa237]

Zhou 2020

Zhou Y, Hou Y, Shen J, Huang Y, Martin Y, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery* 2020;**6**:14. [DOI: 10.1038/s41421-020-0153-3]

APPENDICES

Appendix 1. MEDLINE search strategy

Search	Query
#1	Search "Coronavirus"[Mesh]
#2	Search (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*) Field: Title/Abstract
#3	Search (((respiratory* AND (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") AND (Wuhan* or Hubei* or China* or Chinese* or Huanan*)). Field: Title/Abstract
#4	Search "severe acute respiratory syndrome*" Field: Title/Abstract
#5	Search ((outbreak* or wildlife* or pandemic* or epidemic*) AND (China* or Chinese* or Huanan*)) Field: Title/Abstract
#6	Search (corona* or corono*) AND (virus* or viral* or virinae*) Field: Title/Abstract
#7	Search (((((#1) OR #2) OR #3) OR #4) OR #6)
#8	Search chloroquin* Field: Title/Abstract
#9	Search Hydroxychloroquin* OR Oxychloroquin* Field: Title/Abstract
#10	Search ("Hydroxychloroquine"[Mesh]) OR "Chloroquine"[Mesh]
#11	Search Aralen or Plaquenil Field: Title/Abstract

(Continued)

#12	Search antimalaria* or anti-malaria* Field: Title/Abstract
#13	Search (((#8) OR #9) OR #10) OR #11OR #12
#14	Search (#13) AND #7

This is the preliminary search strategy for MEDLINE (PubMed). It will adapted for other electronic databases. We will report all search strategies in full in the final version of the review.

WHAT'S NEW

Date	Event	Description
22 April 2020	Amended	Amended protocol title and updated Hannah Ryan affiliation details

CONTRIBUTIONS OF AUTHORS

BS and HR wrote the protocol with input from TK, MC, and TF. All protocol authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

BS is a Clinical Research Fellow for the NIHR Global Health Research Group on Brain Infections at the University of Liverpool (No. 17/63/110), and also works at the Royal Liverpool University Hospital, UK, and Christian Medical College, Vellore, India. He has no known conflicts of interest to declare in respect of chloroquine or hydroxychloroquine for management of COVID-19.

HR is a Specialist Registrar in Clinical Pharmacology in Liverpool, and is employed as a full time NHS clinician, and has no conflicts of interest to declare in respect of chloroquine or hydroxychloroquine for management of COVID-19.

TK has no conflicts of interest to declare in respect of chloroquine or hydroxychloroquine for management of COVID-19.

MC has no conflicts of interest to declare in respect of chloroquine or hydroxychloroquine for management of COVID-19.

TF has no conflicts of interest to declare in respect of chloroquine or hydroxychloroquine for management of COVID-19.

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